ENDOCRINOLOGY
Initial self assessment exam

Question 1.
An otherwise healthy 4 year-old boy is less than the 5th percentile for length; his length was at the 10th percentile at 3 years of age. His weight has been at the 10th percentile since birth. Findings on physical examination are unremarkable except for microphallus.

Of the following, the diagnostic study that is MOST likely to establish the etiology of this boy's decline in growth rate is a(n)

A. bone age study  
B. complete urinalysis  
C. examination of stool for ova and parasites  
D. growth hormone stimulation test  
E. sweat chloride test

Question 2.
During the annual physical examination of a 15-year-old girl who is in good health, you detect a 1x2 cm nodule in the right lobe of the thyroid gland.

Which of the following findings INCREASES the likelihood of malignancy in this patient?

A. Adolescent age  
B. Cystic lesion  
C. Exposure to ultraviolet radiation  
D. Mobility of the lesion  
E. Thyrotoxicosis

Question 3.
A 15-year-old girl is concerned about her lack of breast development. Physical examination reveals that the sexual maturity rating for breast and pubic hair development is stage 1.

Of the following, the physical finding that would be MOST suggestive of a central nervous system cause for this girl's pubertal delay is

A. absence of the pectoralis muscle  
B. hypoplasia of the optic nerve  
C. short metacarpal bones  
D. unilateral cleft lip  
E. upper-to-lower segment ratio of 0.80
Question 4.
An 18-month-old infant is seen because the mother is concerned that his legs are bowed. The infant was breastfed until 14 months of age. The mother is 5’ tall, and states that her grandfather was very short.

Of the following, laboratory tests are MOST likely to reveal

A. high circulating parathyroid hormone
B. inadequate reabsorption of phosphate by the kidney
C. inadequate stimulation of bone resorption by parathyroid hormone
D. low conversion of vitamin D to 25-hydroxylase vitamin D
E. poor gastrointestinal absorption of phosphate

Question 5.
Results of newborn screening tests on a term infant at 3 days of age include a filter paper thyroxine (T4) level of 6.9 mcg/dL (normal, >11.5 mcg/dL) and a thyroid-stimulating hormone (TSH) level of 38 mcU/mL (normal, <30 mcU/mL).

Of the following, the MOST appropriate next step in managing this infant is to

A. measure the serum thyroid-binding globulin level
B. observe for symptoms of hypothyroidism
C. obtain a radioisotope scan of the thyroid gland
D. obtain measurement of the free T4, and TSH levels
E. repeat the newborn screening test

Question 6.
A 3-year-old girl has isolated bilateral breast tissue development with no other signs of pubertal development, such as pubic hair. All growth parameters are at the 50th percentile.

Of the following, the MOST appropriate management is to

A. measure serum gonadotropin levels
B. obtain computed tomography of the head
C. obtain pelvic ultrasonography
D. obtain radiography of the hand and wrist to determine bone age
E. reassure the parents that such breast development is probably normal, and see the patient back in 3 months.

Question 7.
An afebrile 5-year-old child has had a generalized seizure. Bedside glucose level is normal. Additional laboratory evaluation reveals: sodium, 138 mg/dL; potassium, 4.3 mg/dL; calcium, 6.5 mg/dL; phosphorus, 7.5 mg/dL; magnesium, 1.7 mEq/L; albumin, 4.0 g/dL; blood urea nitrogen, 8.0 mg/dL; and creatinine, 0.5 mg/dL.

Of the following, the MOST likely cause of this child’s hypocalcemia is:

A. hyperthyroidism
B. hypervitaminosis D
C. hypomagnesemia
D. hypoparathyroidism
E. renal osteodystrophy
Question 8.
You are asked to evaluate an otherwise healthy 17-year-old girl for primary amenorrhea. Her mother and sister began menstruating at age 12. She takes no medications and denies any history of headaches, galactorrhea, nausea or vomiting. Thelarche occurred at age 13. Her breasts are Tanner stage 5, but there is only very scant pubic hair. The bimanual examination reveals a blind vaginal pouch.

Of the following, the study MOST likely to confirm the diagnosis is

A. computed tomography of the head
B. computed tomography of the pelvis
C. serum estradiol level
D. blood karyotype
E. serum prolactin level

Question 9.
A 15-year-old boy is growing at a rate of 5 cm/y. His height and weight have been at the 5th percentile since age 5. His medical history is benign. Physical examination is normal except for absent pubic hair and testicles measuring 1.8 cm in length. His bone age is 12 years. Serum levels of follicle-stimulating hormone and luteinizing hormone are at prepubertal concentrations.

Of the following, the MOST likely diagnosis is

A. constitutional delayed puberty
B. Cushing syndrome
C. hypothyroidism
D. 17-hydroxylase deficiency
E. testicular dysgenesis

Question 10.
A 12-week-old female infant who was born at home has received no medical care. She has a coarse face, with puffy eyelids, thickened protruding tongue, and thick hair. Her cranial sutures are easily palpable, and posterior and anterior fontanelles are open. Her abdomen is protuberant, and an umbilical hernia is present. Her skin is cold to touch and mottled. No masses are palpable in the neck.

Of the following, the MOST likely long-term sequelae of this infant's condition is

A. cerebral palsy
B. corneal opacities
C. deafness
D. hydrocephalus
E. mental retardation
Question 11.
You are asked to evaluate a 9-year-old child who has short stature and obesity. Her weight is at the 95th percentile and her height is at the 5th percentile for age. Reviewing her growth chart you note that she had a normal growth pattern (weight and height at the 50th percentile) until 5 years of age when she began to gain weight dramatically. She has no history of hypotonia as an infant.

Of the following, the MOST likely cause for the change in her growth pattern is

A. Cushing syndrome
B. exogenous obesity
C. hyperthyroidism
D. inflammatory bowel disease
E. Prader-Willi syndrome

Question 12.
You are evaluating an otherwise healthy 15-year-old boy for short stature. He takes no medications and eats a normal diet. His height and weight have been at the 5th percentile since early childhood. Findings on physical examination are normal, with genitalia at sexual maturity rating (Tanner) stage 4.

Of the following, the MOST likely laboratory finding would be

A. a decreased hemoglobin level
B. abnormal thyroxine and thyroid stimulating hormone levels
C. an elevated erythrocyte sedimentation rate
D. bone age that is equivalent to chronologic age
E. elevated serum creatinine concentrations

Question 13.
A healthy 7-year-old girl has bilateral breast tissue development and long, downy, pigmented hair over the labia majora, with a few coarse curly hairs. All growth parameters are at the 50th percentile. Findings on the remainder of the physical examination are normal.

Of the following, the MOST appropriate initial management for this patient is

A. computed tomography of the abdomen
B. computed tomography of the head
C. pelvic ultrasonography
D. radiography of the hand and wrist to determine bone age
E. reassurance of the parents that such secondary sexual development is within the range of normal
**Question 14.**
A 16-year-old otherwise healthy girl presents for evaluation of primary amenorrhea. Physical examination reveals a height of 55.5 in (140 cm), weight of 110 lb (50 kg), no breast tissue and Tanner stage 3 pubic hair development. Her mother’s height is 68 in (173 cm), and her father’s height is 70 in (178 cm).

Of the following, the MOST likely diagnosis is

A. androgen insensitivity (testicular feminization) syndrome  
B. constitutional delay of growth and development  
C. familial short stature  
D. imperforate hymen  
E. Turner syndrome

**Question 15.**
An 18-year-old female college student presents for evaluation of fatigue. She has had difficulties concentrating on her studies and has lost 8 kg since her last visit 1 year ago. Her last menstrual period was 3 months ago. Physical examination reveals a thin woman with a body mass index less than 15%. Her skin is a bronze color, with prominent freckles on her face, dark palmar creases, and dark-pigmented areolae. A urine pregnancy test is negative.

Of the following, the MOST likely diagnosis is

A. Addison disease  
B. Anorexia nervosa  
C. Hyperthyroidism  
D. Late-onset congenital adrenal hyperplasia  
E. Polycystic ovarian syndrome
Careful serial measurements and comparisons of growth parameters, including height, weight, and head circumference, are important in the evaluation of a child who is failing to grow normally. Children who have growth hormone (GH) deficiency, for example, often appear chubby; that is, their weight is proportionately greater than their height when plotted on standard growth curves over time. A thorough physical examination also should be done to detect signs of dysfunction in one or more organ systems that could provide clues to the cause of the failure to thrive. Children who have congenital GH deficiency due to panhypopituitarism often have microphallus; associated findings include small testes and an underdeveloped scrotum.

The most appropriate test to confirm the diagnosis of GH deficiency is a growth hormone assay. A low initial concentration of GH that fails to rise appropriately in response to pharmacologic stimulation tests (eg, infusion of insulin or arginine) would confirm the diagnosis. Any affected child also should be evaluated for hypothyroidism because impaired secretion of thyroid stimulating hormone can be associated with GH deficiency.

A recent study from Italy demonstrated that among infants who have GH deficiency, those who were appropriate size for gestational age had a significantly better response to GH therapy than patients who had been small for gestational age.

A complete urinalysis can demonstrate findings consistent with several different etiologies of failure to thrive: a low specific gravity in patients who have diabetes insipidus; a high urinary pH in the presence of systemic acidosis or renal tubular acidosis; or pyuria or hematuria in patients who have a urinary tract infection. Each of these conditions could result in growth failure, but a small penis, as noted in the patient presented in the vignette, would not be an associated finding.

A sweat chloride test is a noninvasive, inexpensive screening test used to diagnose cystic fibrosis. An abnormal result would be unlikely in a child who has been healthy and who has had no pulmonary symptoms or evidence of gastrointestinal malabsorption.

Examination of the stool may reveal Giardia lamblia, a parasite that can cause malabsorption sufficient to produce poor weight gain. This infection is most likely to occur in a child who is attending child care. A history of bulky, foul-smelling stools and weight loss, however, would be expected associated findings.

Although bone age would be expected to be moderately delayed in a child who has GH deficiency, this is a nonspecific finding and would provide less information than measurement of the GH level.

Thyroid nodules occur less commonly during adolescence than during adulthood, but the incidence of malignancy (carcinoma) in these nodules is higher among adolescents. For example, malignancy has been reported in 12% to 15% of adolescents who have nodules but in only 4% of adults.

Papillary adenocarcinoma is the most common histologic type of thyroid cancer in children and youth; follicular and medullary thyroid carcinoma are much less common. Although a cystic lesion detected by physical examination or ultrasonography is unlikely to be malignant, needle aspiration of the cyst usually is performed to confirm that it is benign. Some surgeons and pediatric endocrinologists prefer surgical excision because aspiration has not been used extensively in adolescents.

Any history of previous ionizing irradiation of the head, neck, or thorax increases the risk for developing thyroid neoplasia, but exposure to ultraviolet radiation would not increase this risk. Rarely, autonomously functioning thyroid nodules produce hyperthyroidism (Plummer disease); such nodules usually are benign.

A lesion that is mobile (ie, not attached to surrounding tissue) is unlikely to be malignant. In contrast, a lesion associated with lymphadenopathy is likely to be malignant.

Breast development (thelarche) usually begins between 8 and 12 years of age. Girls who have no breast development by 13 years of age should be evaluated for hormonal or anatomic conditions that cause delayed or absent breast development. One of the most common causes of delayed thelarche is pubertal delay, which may be due to central nervous system (CNS) disorders or ovarian dysfunction. A CNS cause of pubertal delay should be suspected for the girl described in the vignette if hypoplasia of the optic nerve is noted on funduscopic examination. Many CNS disorders, including absence of the septum pellucidum (septo-optic dysplasia), agenesis of the corpus callosum, and hypopituitarism, are associated with optic nerve hypoplasia. The most common hormonal disorder associated with optic nerve hypoplasia is growth hormone deficiency, although gonadotropin deficiency also may occur.

Ovarian dysfunction occurs in patients who have chromosomal disorders such as Turner syndrome (45X) and other variants (45X/46XX, 46iXp, 45X/46iXq). The ovaries are stimulated by gonadotropin, but cannot produce adequate amounts of estrogen for the breasts to develop normally. Physical findings suggestive of Turner syndrome include short stature, webbed neck, large ears, widely spaced nipples, lymphedema, and short fourth and fifth metacarpal bones.
Unilateral cleft lip and palate usually is an isolated defect that is not associated with either delayed puberty or CNS disorders.

An upper-to-lower segment ratio of 0.80 is abnormal and is more likely to be associated with skeletal dysplasias resulting from short limbs than with short stature due to hypopituitarism or Turner syndrome. Thus, this feature is not associated with CNS anomalies that could result in pubertal delay.

A rare cause of absent breast development is amastia or the absence of breast tissue. This anomaly was described by Poland in 1841 and is characterized by the unilateral absence of the pectoralis muscle, nipple, and areola as well as ipsilateral upper limb deformities such as syndactyly, oligodactyly, and distal hypoplasia of the arm. This anomaly is thought to be caused by diminished blood flow to the affected side during early fetal development. The condition can be distinguished from delayed breast development due to hormonal causes because of its associated limb and chest anomalies and the unilateral, rather than bilateral, absence of breast development. Lastly, amastia does not affect the timing of genital development.

**Critique 4**

**Preferred Response: B**

Any child who has hypophosphatemia requires a thorough evaluation because phosphate is essential for energy production and for bone growth and development. The kidney plays a major role in maintaining therapeutic levels of serum phosphate by reabsorbing about 85% to 90% of the filtered phosphate during the first few years of life.

Rickets is a general term used to describe bony malformation due to any abnormality in the production or excretion of calcium and phosphate. Any child who has clinical evidence of growth retardation or rickets in the presence of a low serum phosphate level should have serum levels of calcium, parathyroid hormone (PTH), 25-hydroxyvitamin D, and 1,25 dihydroxyvitamin D (1,25(OH)2D) measured. These values will provide clues to the etiology of the growth failure.

The most common form of inherited rickets is X-linked hypophosphatemic rickets (X-hyp). Children who have this disorder develop hypophosphatemia due to renal wasting of phosphate. The precise mechanism (transport protein abnormality) has not yet been elucidated. Regardless, there is high urinary excretion of phosphate and simultaneous low serum phosphate concentrations. The leak most likely occurs in the renal proximal tubule. Serum calcium and PTH levels are normal. Furthermore, serum 1,25(OH)2D levels are also “normal”. It has been suggested that part of the problem in X-hyp may be due to inadequate stimulation of 1,25(OH)2D synthesis in the kidney in the face of low serum phosphate. Given that one role of 1,25(OH)2D is to stimulate reabsorption of phosphate in the GI tract, a compensatory increase in its levels in children who have low serum phosphate levels is expected. Thus, the abnormality in X-hyp appears to be inadequate reabsorption of phosphate by the renal proximal tubule in combination with inappropriate levels of 1,25(OH)2D synthesis by the kidney.

If left undetected or untreated, X-hyp will result in rickets and often linear growth failure. Administration of neutral phosphate is necessary to increase the serum phosphorous to levels above 3.5mg/dL. Relatively small doses of 1,25(OH)2D are needed. With this regimen, many children can achieve improved growth and healing of rickets.

It is essential to recognize other causes of hypophosphatemic rickets in children. Hereditary hypophosphatemic rickets with hypercalcuria is a rare disorder in which hypophosphatemia is associated with increased levels of 1,25(OH)2D. There appears to be a compensatory mechanism in response to low serum phosphate levels in children who have this disorder. Following the elevated serum levels of 1,25(OH)2D, serum PTH levels are suppressed, leading to hypercalcuria due to reduced stimulation of renal reabsorption of calcium. Adolescent hypophosphatemic rickets closely resembles X-hyp but occurs much later in childhood. The treatment is identical to that currently used for X-hyp. Finally, an autosomal dominant mild form of hypophosphatemic rickets usually responds to either minimal or low doses of phosphate and 1,25(OH)2D.

**Critique 5**

**Preferred Response: D**

Screening of newborn infants for hypothyroidism is performed routinely in every state and many foreign countries. Congenital hypothyroidism, the most commonly detected defect, occurs in 1 per 3,000 to 4,000 infants. Screening is designed to distinguish infants who are likely to have the disorder from those who likely do not have it. However, it is not the definitive test for diagnosis. Cutoff levels for screening are established to minimize false-negative findings ("negativity in disease") at the expense of an increased number of false-positive findings ("positivity in health"). Two-tier screening (eg, initial measurement of the serum thyroxine [T4] with measurement of thyroid stimulating hormone [TSH] to follow only on that sample of infants who have a T4 level <10th percentile) is used widely in the United States. Other risk factors, such as birthweight and gestational age, also should be considered. For example, preterm infants, especially those of very low birthweight, have low levels of T4 more commonly than do term infants.

If the results of a newborn screening test are suggestive of hypothyroidism, confirmatory and diagnostic testing must be performed immediately before instituting treatment. Overtreatment with thyroxine in an infant who does not have hypothyroidism may result in craniosynostosis, hyperactivity, and intellectual impairment. When the T4 level is low but the TSH level is only mildly elevated (eg, 28 mcU/mL, as in the infant in the vignette), true hypothyroidism is unlikely. Indeed, the TSH level in a term infant who has agenesis of the thyroid gland usually exceeds 100 mcU/mL and often is greater than 200 mcU/mL. However, partial thyroid deficiency, as might be seen with a small ectopic gland or an inborn error of hormonogenesis, may yield borderline results, such as those reported for the infant in the vignette.

Obtaining another measurement of both the T4 and the TSH levels is the first step in confirming a diagnosis of hypothyroidism and determining whether treatment is necessary. It would not be necessary to repeat the newborn screening test, and this might cause additional delay.
Any child who has a low T4 level and a TSH concentration greater than 40 mcU/L is considered to have primary hypothyroidism. Treatment with replacement l-thyroxine should be initiated before results of the confirmatory tests are available.

An infant who has a low level of T4 and a normal level of TSH probably has a deficiency of thyroid-binding globulin; measurement of thyroid-binding globulin and free T4 can help make the diagnosis.

The serum protein level is low in the small preterm infant, which often leads to a low T4 level in the serum despite the absence of pathologic changes in the thyroid. Some very-low-birthweight infants who have low T4 levels and normal TSH levels recover spontaneously. No cause for these findings is apparent except for the prematurity.

Investigation and treatment of thyroid abnormalities never should be delayed until symptoms develop. Only about 10% of infants who have hypothyroidism are symptomatic during the neonatal period. Hyperbilirubinemia, lethargy, umbilical hernia, constipation, and poor weight gain are associated with hypothyroidism, but these findings are nonspecific. A radioisotope scan rarely is obtained prior to treatment, but it may be useful in distinguishing agenesis of the gland from dys hormonogenesis as the cause of hypothyroidism.

**Critique 6**

**Preferred Response: E**

Puberty involves an increase in production of both gonadal and adrenal steroids. It is characterized by an increase in growth rate and the appearance of secondary sex characteristics. However, the onset of the hormonal changes of puberty precede any physical changes by a few years.

In females, puberty usually begins between the ages of 8 and 13 and is completed, on the average, in 4.2 years, with a range of 1.5 to 6 years. In most boys, puberty begins between the ages 9 and 14 and is completed in 3.5 years, with a range of 2 to 4.5 years.

The onset of pubertal changes at an earlier age may be a variation of normal or an indication of sexual precocity. The strict definition of precocious puberty is the appearance of pubertal signs before age 8 in a girl or before age 9 in a boy. In the young female, this involves both breast and pubic hair development and in the young male, both pubic hair and genital development.

Premature thelarche is isolated breast development in girls younger than 8 years of age and usually occurs between 1 and 4 years of age. It is a variation of normal pubertal development due to transient elevations in estrogen levels from either functional ovarian cysts or fluctuations in pituitary gonadotropin secretion. The breast enlargement usually is bilateral and occurs without nipple and areolar development or other estrogen effects, such as an increase in uterine size, as seen in the girl in the vignette. There is neither pubic hair development nor linear growth acceleration associated with this condition. A possible exposure to medications, such as estrogen-based creams or oral contraceptives, is important to elicit in a history. The hallmark of premature thelarche is nonprogression of secondary sexual characteristics and spontaneous regression of breast enlargement. Accordingly, the parents of the child in the vignette can be reassured that no further studies such as gonadotropin levels, computed tomography, pelvic ultrasonography, or bone age determination is required.

Premature pubarche is another variation of normal pubertal development that can be seen in boys and girls before the age of 8 years. It is due to early activation of adrenal androgens and is manifested clinically as the isolated appearance of pubic hair. Axillary hair and axillary odor also may be present, but there are no other signs of pubertal development (eg, breast enlargement) or virilization. It is a benign condition, but adrenal tumors and mild forms of congenital adrenal hyperplasia must be ruled out in the evaluation.

**Critique 7**

**Preferred Response: D**

The child described in the vignette had a generalized seizure without fever. A thorough history and physical examination as well as measurement of a complete metabolic panel and: phosphorus, magnesium, and parathyroid hormone often provides sufficient information to narrow the etiology to a limited number of diagnoses.

A low calcium level in the presence of a normal serum albumin level, as described in the vignette, is consistent with ionized hypocalcemia as the cause of the seizure. Patients who have hypomagnesemia also can present with hypocalcemia and hypoparathyroidism. Treatment with magnesium normalizes the serum calcium levels in these cases. However, the magnesium levels are normal in this patient.

Patients who have hyperphosphatemia, hypocalcemia, normal magnesium levels, and low parathyroid hormone levels usually have some form of hypoparathyroidism. The DiGeorge anomaly is manifested by variable deficiencies of thymic (cell-mediated) immunity and parathyroid gland function (hypoparathyroidism) as well as anomalies of the face and cardiovascular system. Facial features include micrognathia, hypertelorism, short philtrum, and malformed or low-set ears. The most common heart lesions include truncus arteriosus and aortic arch syndromes.

Autoimmune destruction of the parathyroid glands also can occur. Children who have the polyglandular autoimmune syndrome type I or autoimmune polyendocrinopath–candidiasis–ectodermal dystrophy (APECED) can present with mucocutaneous candidiasis and a variety of other autoimmune disorders, including hypoadrenalism, hypoparathyroidism, hypothyroidism, hypogonadism, vitiligo, and diabetes mellitus. However, hyperthyroidism is not associated with hypocalcemia or hypoparathyroidism.

Pseudohypoparathyroidism involves an end-organ resistance to parathyroid hormone and, thus, is associated with hypocalcemia and elevated parathyroid hormone levels. Characteristic features include moon facies, brachydactyly, short
stature, obesity, and developmental delay. Chronic renal failure can cause hypocalcemia and renal osteodystrophy, but normal renal function studies make this unlikely. It is associated with increased serum phosphorus concentrations and elevated levels of parathyroid hormone. Vitamin D deficiency states, rather than hypervitaminosis D, also can cause hypocalcemia in the presence of elevated parathyroid hormone levels.

Critique 8

Preferred Response: D

Most teens have menarche within 2 to 2.5 years after thelarche or within 1 year of attaining full physical maturity. The presence of primary amenorrhea and normal secondary sexual characteristics at age 17 in the otherwise healthy adolescent girl described in the vignette warrant further evaluation.

There are numerous causes of primary amenorrhea, but not all need to be considered in a patient who has mature secondary sexual characteristics. Although her external genitalia are phenotypically female, the presence of a blind vaginal pouch is most consistent with the diagnosis of male pseudohermaphroditism. A serum karyotype will confirm this diagnosis.

Complete testicular feminization is the most common cause of male pseudohermaphroditism (phenotypic female who has 46,XY karyotype and with testes) and results from androgen insensitivity. Not all affected individuals present with ambiguous genitalia because the spectrum of sensitivity is broad. If the receptor to androgens in nonfunctional or absent, the external genitalia will be those of a normal female. The diagnosis is usually delayed until the absence of menses bring the adolescent to medical attention. Internal female genitalia do not form because the mullerian ducts regress under the effects of mullerian inhibiting factor produced by occult male gonads located in the abdomen. However, low levels of gonadal and adrenal estrogens, unopposed by androgens, allow breast development to occur in affected individuals.

Signs and symptoms of male pseudohermaphroditism are variable, depending on the etiology. As described previously, the phenotypic female may present with primary amenorrhea or an infant may have ambiguous genitalia noted at birth. The otherwise healthy teenage who has androgen insensitivity may have sparse axillary and pubic hair, normal breast development and a blind vaginal pouch with absence of the ovaries, uterus and fallopian tubes. Testes and normal male levels of testosterone are present.

Because the adolescent described in the vignette does not have a central cause of amenorrhea, CT of the head is unnecessary. Furthermore, MRI is the study of choice to visualize the pituitary gland. CT of the pelvis may confirm the absence of internal female genitalia, but will not make the diagnosis. A serum estradiol level is unnecessary in the adolescent who has mature breast development. A serum prolactin level is also not indicated because the primary amenorrhea clearly stems from abnormal genital anatomy.

Critique 9

Preferred Response:

Although the actual incidence of delayed sexual development does not differ appreciably by gender, clinicians are confronted by more boys who have the complaint than girls. Concern about delayed puberty is warranted in males when testicular length does not exceed 2.5 cm by age 14 and in females if breast development has not occurred by 13 years or menses have not begun by age 15 years. Most of these adolescents, including the boy described in the vignette, will have physiologic or constitutional delayed puberty.

A careful history and physical examination can be helpful in arriving at a diagnosis in patients suspected of having pubertal delay. Adolescents who have constitutional delayed puberty typically exhibit a growth pattern suggestive of constitutional delayed growth. There usually is a history of short stature since late infancy in conjunction with a normal growth velocity (5 cm/y). Bone age typically is delayed and is consistent with the height age. Frequently, there is a positive family history of a parent or sibling who developed slowly and did not achieve full height until the late teen years.

A thorough history should look for clues suggesting other conditions that may be associated with growth problems, such as chronic illness, eating disorders, hypothyroidism, strenuous exercise, drug abuse, hypopituitarism, hypopituitarism, Turner syndrome, or Klinefelter syndrome. Patients who have Cushing syndrome usually have a normal growth pattern until they become symptomatic, at which time they develop increased weight gain and decreased growth velocity. In patients who have hypothyroidism, a decrease in growth rate from baseline also is accompanied by an increase in weight gain.

Laboratory studies can be helpful in evaluating patients who have suspected pubertal delay. A basic evaluation should include a urinalysis, complete blood count, erythrocyte sedimentation rate, lateral skull radiography to evaluate the pituitary fossa, bone age determination, and thyroid function tests. Girls who exhibit significant short stature also should have a karyotype performed to exclude Turner syndrome. Measurement of serum gonadotropins (ie, follicle-stimulating hormone, luteinizing hormone) can be very helpful; adolescents who have constitutionally delayed puberty will have prepubertal gonadotropin levels, as was found in the boy described in the vignette. In contrast, elevated gonadotropin levels should suggest a variety of other conditions, including ovarian or testicular dysgenesis; 17-hydroxylase deficiency in the male or female; 17-ketosteroid reductase deficiency in the genetic male; testicular feminization due to androgen insensitivity; or bilateral gonadal failure due to trauma, infection, irradiation, or chemotherapy.

When possible, treatment of adolescents who have delayed development should be directed at the underlying cause. Patients who have constitutional delayed puberty should be reassured that they are normal and will develop without intervention. Short-term treatment with testosterone can be helpful in males who have not exhibited any signs of significant masculinization by 14 to 15 years and whose emotional well-being is affected adversely by this delay. However, bone age
should be monitored carefully whenever endogenous androgens are administered. Short-term treatment with low-dose estrogens may be helpful in girls whose pubertal development is delayed markedly.

**Critique 10**

**Preferred Response: E**

The infant described in the vignette has physical findings that are most consistent with congenital hypothyroidism. Because the infant was born at home and has received no medical care, it is likely that no neonatal screening for congenital hypothyroidism was performed and that the disorder has gone untreated for the first 12 weeks of life. The most likely long-term consequence of untreated congenital hypothyroidism is mental retardation.

The overall incidence of congenital hypothyroidism, based on neonatal screening programs in North America, is estimated to be 1 in 4,000 live births. The incidence among Hispanic infants is increased (1 in 3,000) and decreased among both Caucasian (1 in 5,000) and African-American (1 in 32,000) infants. Females are twice as likely to be affected. Although the occurrence of the disorder usually is sporadic, familial cases have been described.

Congenital hypothyroidism is caused by thyroid dysgenesis, thyroid dysshormonogenesis, or an abnormality of the hypothalamic-pituitary axis. Thyroid dysgenesis refers to an incomplete development of the thyroid gland, which varies from complete absence to hypoplasia. Ectopic thyroid gland usually is hypoplastic. Thyroid dysshormonogenesis refers to a hereditary defect in the synthesis or metabolism of thyroid hormone. Goiter may be noted at birth in infants who have thyroid dysshormonogenesis or it may develop later in life. Thyroid dysfunction that results from ineffective stimulation of thyroid hormone synthesis by thyroid-stimulating hormone (TSH) is known as pituitary or secondary hypothyroidism. Abnormalities in thyrotropin-releasing hormone (TRH) result in hypothalamic (or tertiary) hypothyroidism.

An infant suspected of having congenital hypothyroidism requires prompt evaluation, including a history, physical examination, and laboratory testing. If hypothyroidism is suspected, thyroid hormone replacement therapy should be initiated promptly while awaiting test results because the adverse central nervous system (CNS) effects of thyroid hormone deficiency are most critical in the first year of life. The diagnosis is confirmed by measurements of plasma thyroxine and TSH levels. Other laboratory tests, including radionuclide scanning, can provide information concerning the function and anatomy of the thyroid gland. The goal of therapy is to normalize plasma thyroid hormone levels.

Mental retardation in patients who have untreated congenital hypothyroidism varies in severity, depending on residual thyroid function. Delay in the onset of treatment is associated with a decrease in the intelligence quotient. Other signs of CNS dysfunction often are present, including impairment of arithmetic skills, speech, and fine motor coordination.

Cerebral palsy is not a common consequence of untreated congenital hypothyroidism. Most cerebral palsy is due to hypoxic-ischemic injury to the developing brain as a result of antenatal, intrapartum, or postnatal asphyxia.

Eye abnormalities in infants who have untreated congenital hypothyroidism include thickened eyelids and hypertelorism, but corneal opacities are not characteristic. Deafness is not associated with untreated congenital hypothyroidism. Hydrocephalus is an uncommon finding in infants who have not been treated for congenital hypothyroidism.

**Critique 11**

**Preferred Response: A**

The child described in the vignette has a growth pattern that is normal until 5 years of age, when the weight increases dramatically to the 95th percentile and the height decreases to less than the 5th percentile. This is most consistent with an endocrine disorder, either Cushing syndrome or hypothyroidism. Cushing syndrome is caused by persistent elevation of plasma cortisol levels. The most common cause in children is exogenous corticosteroid therapy. Less common endogenous causes include adrenocorticotropic hormone (ACTH)-dependent hypercortisolism and autonomous adrenal hyperfunction. Excessive secretion of ACTH usually results from pituitary adenomas or, rarely, ectopic production of ACTH. Causes of unregulated adrenal hypercortisolism include adrenal adenomas and carcinomas, primary adrenocortical nodular dysplasia, or macronodular adrenal hyperplasia.

Cushing syndrome should be considered in any child who exhibits short stature and obesity. Most children who have exogenous obesity have normal growth velocity (in a prepubertal child, 5 cm/y), follow along a consistent percentile on a growth curve, and typically have a height at the 50th percentile or higher. In contrast, children who have Cushing syndrome exhibit a dramatic change in growth pattern, with a marked increase in weight and a simultaneous decrease in linear growth. Clinical features include central obesity, hypertension, a buffalo hump, hirsutism, striae, acne, easy bruising, and neuropsychiatric changes. Laboratory and radiologic findings that suggest hypercortisolism include hypokalemia, leukocytosis, and decreased bone density. Exogenous hypercortisolism often can be diagnosed based on the history. Patients who have endogenous hypercortisolism should have elevated plasma cortisol levels and increased 24-hour urinary excretion of free cortisol. Measurement of ACTH levels and the suppression of cortisol secretion following the administration of dexamethasone can help identify the underlying cause for the hypercortisolism.

A child who has hypothyroidism could have a growth pattern similar to that seen with Cushing syndrome, but hyperthyroidism usually results in weight loss and an increased growth velocity. Inflammatory bowel disease and other chronic diseases may be associated with slowed growth velocity, but also should be accompanied by weight loss. Children who have Prader-Willi syndrome can develop marked exogenous obesity due to their compulsive eating. This eating pattern usually begins at age 2 to 4 years, but it can be controlled through strict regulation of food intake. Children who have Prader-Willi syndrome often are short for age, but they do not exhibit a dramatic drop-off in growth that is temporally related to a weight gain.
Critique 12

Familial short stature (FSS) is one of the most common causes of short stature and is characterized by deceleration of linear growth during the first 2 or 3 years of life. It is a normal variation in growth, in sharp contrast to the multiple pathologic entities that also can cause growth retardation. Pathologic causes of short stature include endocrinopathies (growth hormone deficiency, hypothyroidism); renal disease (renal tubular acidosis, renal failure); inadequate caloric intake; chronic illness; metabolic bone disease (rickets); chromosomal abnormalities (Turner syndrome and trisomy 21); and specific disorders that may be associated with intrauterine growth retardation, including fetal alcohol syndrome, Russell-Silver syndrome, and Prader-Willi syndrome.

The adolescent described in the vignette most likely has FSS because he is otherwise healthy, takes no medications, and eats a normal diet. The completely normal findings on the physical examination, except for his short stature and weight, are consistent with the diagnosis. Most children who have familial, or genetic, short stature are of normal birthweight and length; other factors are believed to influence birth size more than parental height, such as maternal health, nutrition, and uterine size. During the first 2 years of life, however, most children who have FSS will cross linear growth percentiles downward to their genetic-appropriate linear growth potential. They then continue to experience normal growth below but parallel to the 5th percentile during prepubertal years. The onset and progression of puberty occurs at the expected chronologic age. Although final adult height is short, it is appropriate for parental heights. Bone age typically is equivalent to chronologic age in FSS.

During puberty, the hemoglobin should be increased rather than decreased in an otherwise healthy adolescent male who has no evidence of chronic disease. This increase is due to increased levels of circulating androgens. Abnormal thyroxine and thyroid stimulating hormone levels would suggest hypothyroidism as the etiology for an adolescent's short stature. However, results of this patient's examination are not consistent with this diagnosis because he seems to be progressing through puberty normally. Other abnormal laboratory studies, such as an elevated erythrocyte sedimentation rate and serum creatinine concentration, would suggest the presence of a chronic illness of which there are no other indications for the adolescent in the vignette.

Critique 13

The physical examination findings of the child described in the vignette are consistent with a diagnosis of precocious puberty. Strictly defined, precocious puberty is the appearance of signs of pubertal maturation before age 8 in a girl or before age 9 in a boy. It is characterized by an increase in secretion of gonadal steroids that prompts increased height velocity and somatic development, including the appearance of secondary sexual characteristics. In the young female, this involves development of both breasts and pubic hair and in the male, development of pubic hair and genitals.

True or central precocious puberty is due to early maturation of hypothalamic secretion of gonadotropin-releasing hormone (GnRH). In females, a search for an underlying abnormality of the central nervous system (CNS) may be undertaken, although many of these cases are idiopathic and have no definable CNS cause. In contrast, a pathologic cause for precocious puberty is identified in 90% of males. “Pseudocomplete” forms of precocious puberty include gonadotropin-secreting tumors such as a teratoma or hepatoblastoma; gonadal tumors (ovarian or testicular); adrenal tumors; hypothyroidism; iatrogenic or exogenous exposure to estrogen-containing drugs, including creams and makeup; and specific syndromes such as McCune-Albright syndrome.

When precocious puberty is suspected, the history should focus on the chronology of secondary sexual development, the growth pattern, any intercurrent illness, drug ingestion, and head trauma. The evaluation should include a careful assessment of the child's sexual maturity rating or Tanner stage and growth velocity as well as a detailed neurologic and ophthalmologic examination. Signs of hypothyroidism or estrogen stimulation also should be noted. The abdomen and testicles should be examined for any masses.

For most children who have precocious puberty, evaluation should begin with radiography of the hand and wrist to determine bone age. A normal bone age indicates an incomplete form of sexual precocity, and the clinician should observe the patient for 6 to 12 months to determine whether complete precocious puberty or another condition is developing. A retarded bone age suggests hypothyroidism, and an advanced bone age requires further investigation with a GnRH stimulation test to differentiate between true precocious puberty and the “pseudocomplete” form.

Computed tomography of the abdomen or head and pelvic ultrasonography are indicated only if the bone age is advanced. Reassurance of the parents that the secondary sexual development reported for the girl in the vignette is normal is inappropriate because of her young age.

Critique 14

The girl in the vignette has primary amenorrhea, defined as the absence of menses by age 14 years in a patient who has no secondary sexual characteristics (eg, breast development) or by 16 years when such characteristics are present. She has short stature, normal weight, absent breast tissue (suggesting an absence of ovarian estrogen), and normal pubic hair (confirming the presence of adrenal androgens). These clinical findings are characteristic of gonadal dysgenesis caused by Turner syndrome. Gonadal dysgenesis is the most common cause of primary amenorrhea, and Turner syndrome is the most common cause of gonadal dysgenesis.

Measurement of FSH and LH concentrations is useful in determining the cause of primary amenorrhea. Elevated FSH and LH levels (hypergonadotropic hypogonadism) usually reflect ovarian dysgenesis but rarely are due to premature ovarian
failure, resistant ovary syndrome, or the effects of chemotherapy or radiation therapy. Low levels indicate a hypothalamic or pituitary disorder (hypogonadotropic hypogonadism). Chromosomal analysis should be performed when FSH and LH levels are elevated.

Individuals who have androgen insensitivity (testicular feminization) syndrome are chromosomally male (XY genotype) and have male gonads that produce normal amounts of testosterone. However, because the androgen receptors do not function normally, male external genitalia do not develop and, in contrast to the patient in the vignette, pubic and axillary hair are sparse. Affected individuals have normal stature and breast development.

The most common cause of pubertal delay is constitutional delay of growth and development, which often is familial and occurs more commonly in boys. Height, pubertal development, and bone age are delayed by 2 to 4 years. Unlike the girl in the vignette, the appearance of sexual hair and breast development are delayed in patients who have constitutional delay. Individuals who have familial short stature do not experience pubertal delay and have a compatible family history. Finally, although an imperforate hymen is one cause of primary amenorrhea, affected patients have normal pubertal progression and are of normal height.

**Critique 15**

**Preferred Response: A**

Addison disease, the result of autoimmune destruction of the adrenal gland, usually presents as slowly evolving manifestations of deficiencies in cortisol, aldosterone and sex steroid hormones. The onset is characterized by anorexia, weight loss, muscle weakness and fatigue. The blood pressure may be low. The patient may have complaints of nausea, vomiting, diarrhea, or abdominal pain and may also crave salt. The clinical finding of increased pigmentation of the skin (e.g., accentuation of freckles, dark palmar creases, bluish-brown buccal mucosa, pigmentation of the skin over the extensor surfaces of the elbows and knees, or a persistent sun tan), as described for the girl in the vignette, should prompt an assessment for Addison disease.

Laboratory findings of hypoglycemia, hyponatremia or hyperkalemia, normochromic anemia, or eosinophilia support the diagnosis of Addison disease. The disease is characterized by a decreased level of cortisol and aldosterone and a high serum ACTH level. The most definitive diagnostic test is an ACTH stimulation test. In patients who have Addison disease, resting levels of cortisol are low, and there is no increase after IV administration of ACTH. If there is a need to differentiate prolonged adrenal suppression from ACTH deficiency, an increase in urinary 17-hydroxycorticosteroid after 3 days of IM ACTH indicates adrenal reactivation, suggesting deficiency of either ACTH or corticotropin-releasing factor. A lack of response confirms the diagnosis of Addison disease.

Addison disease may occur as a part of the polyglandular autoimmune syndromes. Type I is characterized by mucocutaneous candidiasis, hypothyroidism, and Addison disease. It is an autosomal recessive disorder that involves chromosome 21Q22.3. Type II is characterized by an autoimmune hypothyroidism, type I diabetes and Addison disease. Type II has been associated with HLD-DR3 and LKA-DR4.

An adrenal crisis (hypoglycemia, hyponatremia, hyperkalemia, acidosis and hypotension that may progress to shock) may develop if the slowly progressive deficiency is not recognized. Crises may be precipitated by the stress of infection, trauma, surgery, or medications, including thyroid hormone and insulin in both the unrecognized patient or patients who have inadequate glucocorticoid replacement.

Management of an adrenal crisis requires immediate intervention to prevent a fatal outcome. Pretreatment blood samples should be obtained for measuring serum cortisol, ACTH, renin, and aldosterone to confirm the diagnosis. Intravascular volume and renal perfusion must be restored with NS plus sufficient glucose to correct hypoglycemia. Glucocorticoid replacement is administered as an IV bolus of hydrocortisone.

In patients who have significant hyperkalemia (potassium > 6 mEq/L), careful EKG monitoring is necessary. Administration of an oral resin of Kayexalate also is recommended. Dangerously high levels of potassium are treated with IV 10% calcium gluconate.

Patients who have anorexia nervosa and hyperthyroidism may present with weight loss and menstrual irregularities, but they would not have the skin pigment changes reported for the girl in the vignette. Late-onset CAH and PCOS may present with menstrual cycle irregularities and evidence of androgen excess, but the clinical findings of hyperpigmentation should raise the suspicion of adrenal cortisol deficiency. Acanthosis nigricans, a slightly palpable, velvety hyperpigmentation in the intertriginous areas of the body and neck, may be found in patients who have PCOS and may indicate insulin resistance.